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October 27, 2003

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APPLICATION NUMBER: *60/416,911*
FILING DATE: *October 09, 2002*

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SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

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60/416911 . 100902

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Wayne, R.	Danter	147 Chesham Ave., London, Ontario N6G 3V2, Canada

☐ *Additional inventors are being named on the ____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

PROTEIN TYROSINE KINASE INHIBITORS

CORRESPONDENCE ADDRESS

Direct all correspondence to:

☒ Customer Number 24223 →

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PATENT & TRADEMARK OFFICE

☒ Firm or Individual Name	Lola A. Bartoszewicz				
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City	Toronto	State	Ontario	ZIP	M5G 1R7
Country	Canada	Telephone	416 595 1155	Fax	416 595 1163

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages*	21	☐ CD(s), Number	
☐ Drawing(s) *Number of Sheets*		☒ Other (specify)	Fee Transmittal for FY 2002
☒ Application Data Sheet. See 37 CFR 1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

		FILING FEE AMOUNT ($)
☒	Applicant claims small entity status. See 37 CFR 1.27.	
☐	A check or money order is enclosed to cover the filing fees	
☒	The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 192253	$80.00
☐	Payment by credit card. Form PTO-2038 is attached.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

☐ Yes, the name of the U S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Lola A. Bartoszewicz

TELEPHONE 416 595 1155

Date 10/08/2002

REGISTRATION NO. 43394 *(if appropriate)*

Docket Number: 11757-2 LAB

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision

☒ Applicant claims small entity status See 37 CFR 1 27

TOTAL AMOUNT OF PAYMENT **$80.00**

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Wayne R. Danter
Examiner Name	
Group Art Unit	
Attorney Docket No	11757-2 LAB

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money ☐ Other ☐ None

☒ Deposit Account

Deposit Account Number: 192253

Deposit Account Name: Sim & McBurney

The Commissioner is authorized to: *(check all that apply)*

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	80.00
				SUBTOTAL (1)	$80.00

2. EXTRA CLAIM FEES FOR UTILITY AND

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** = 0	X =	0.00
Independent Claims		- 3** = 0	X =	0.00
Multiple Dependent			=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent
				SUBTOTAL (2) $0.00

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non - English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR § 1 17(q)	
126	180	126	180	Submission of Information Disclosure Statement	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1 129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1 129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3)

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Lola A. Bartoszewicz	*Registration No (Attorney/Agent)*	43394	*Telephone*	416 595 1155 ext 200
Signature				*Date*	October 8, 2002

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60/416911 .100902

TRANSMITTAL LETTER (General - Patent Pending)	Docket No. 11757-2 LAB

In Re Application Of:

Wayne R. Danter

Serial No.	Filing Date	Examiner	Group Art Unit

Title:

PROTEIN TYROSINE KINASE INHIBITORS

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

Transmitted herewith is:

Provisional Application for Patent Cover Sheet
Application Data Sheet
Fee Transmittal for FY 2002
Specification - 21 pages

in the above identified application.

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Signature

Dated: **October 8, 2002**

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Cheryl Alphonso

Signature of Person Mailing Correspondence

Cheryl Alphonso

Typed or Printed Name of Person Mailing Correspondence

CC:

Initial Information Data Sheet

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Application Information

Title Line One::	Protein Tyrosine Kinase Inhibitors
Total Drawing Sheets::	
Formal Drawings::	
Application Type::	Utility
Docket Number::	11757-2 LAB

Representative Customer Number::	24223
Registration Number::	43394

[redacted]

Protein Tyrosine Kinase Inhibitors

Field of the Invention

The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction and methods of using such compounds to treat tyrosine kinase-dependent diseases and conditions in mammals.

Background of the Invention

Throughout this application, various references are cited in parentheses to describe more fully the state of the art to which this invention pertains. The disclosure of these references are hereby incorporated by reference into the present disclosure.

Tyrosine kinases are a class of enzymes that catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. Tyrosine kinases are believed, by way of substrate phosphorylation, to play critical roles in signal transduction for a number of cell functions. Though the exact mechanisms of signal transduction is still unclear, tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation.

Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

The receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. Approximately, 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily is comprised of EGFR, HER2, HER3, and HER4. Ligands of this subfamily of receptors include epithelial growth factor, TGF-α, amphiregulin, HB-EGF,

betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-α and β receptors, CSFIR, c-kit and FLK-II. The FLK family is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1) (Plowman et al., DN&P 7(6):334-339, 1994, which is hereby incorporated by reference).

The non-receptor type of tyrosine kinases are also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis (Bolen Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference).

Both receptor-type and non-receptor type tyrosine kinases are implicated in cellular signalling pathways leading to numerous pathogenic conditions, including a variety of cancers. For example, the Bcr-Abl tyrosine kinase is the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). Inappropriate Bcr-Abl activity is also demonstrated in murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Drug screening has been used *in vitro* to try and identify new compounds with potential cell line-specific anti-tumour activity. Such a screening was published with respect to the compound 2,5-pyridinedicarboxamide, N,N'-bis[4-(1,4,5,6-tetrahydro-5-methyl-2-pyrimidinyl)phenyl]-, dihydrochloride (also known as 2,5-pyridinedicarboxanilide, 4'4"-bis(1,4,5,6-tetrahydro-5-methyl-2-pyrimidinyl)-, dihydrochloride trihydrate) (National Cancer Institute 1965)

which was not identified as a protein tyrosine kinase inhibitor. The screening conducted using a leukemia mouse model was not conclusive.

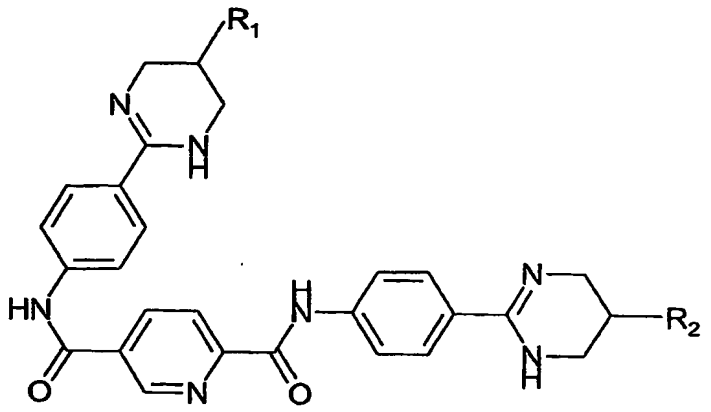
It is has now been identified that the aforementioned compound herein referred to as "COTI-001" is involved in the signal transduction of tyrosine kinases and in particular those tyrosine kinases involved in various malignancies leading to the use of such compound in methods to effectively treat a variety of cancers in mammals.

Summary of the Invention

The present invention relates to the identification of the role of COTI-001 to inhibit, regulate and/or modulate tyrosine kinase signal transduction to treat tyrosine kinase-dependent diseases and conditions, such as cancer and tumour growth, and the like in mammals.

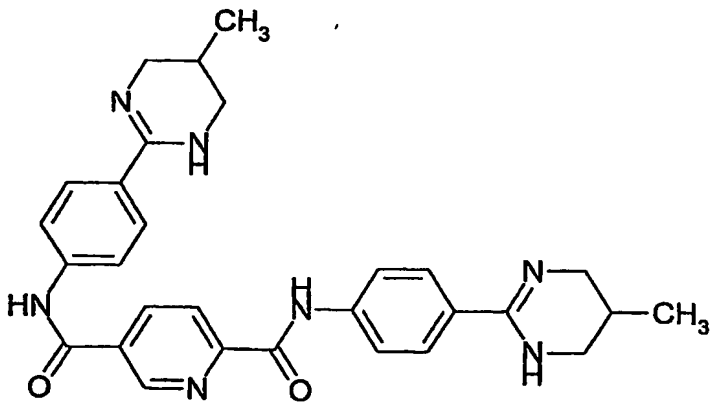
More particularly, the present invention relates to COTI-001 compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds are novel protein tyrosine kinase inhibitors useful in the treatment of a variety of malignancies involving inappropriate tyrosine kinase activity.

One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts and stereoisomers thereof:



wherein R_1 and R_2 are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl; NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl.

In one aspect of the present invention, the compound is represented as formula II:



and the pharmaceutically acceptable salts and stereoisomers thereof.

According to another aspect of the present invention is a pharmaceutical composition which is comprised of a compound in accordance with formula I together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is a pharmaceutical composition which is comprised of a compound in accordance with formula II together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is a method of treating or preventing cancer involving inappropriate tyrosine kinase activity in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of formula I or II.

According to another aspect of the present invention is a method of treating cancer or preventing cancer using a composition comprising a compound of formula I or II wherein the cancer is selected from cancers of the breast, leukemias, melanoma, stomach, colon, CNS, ovarian and prostate and those listed in Table I.

According to still another aspect of the present invention is a method of treating or preventing cancer comprising administration of a therapeutically effective amount of a composition comprising a compound of formula I or II wherein the cancer is chronic myelogic leukemia (CML).

According to another aspect of the present invention is a method of treating or preventing a tyrosine kinase-dependent disease or condition which comprises administering a therapeutically effective amount of a compound selected from the group consisting of formula I and formula II.

According to another aspect of the present invention is the use of a compound of formula I and/or II in a medicament for the treatment of a disease condition involving inappropriate tyrosine kinase activity.

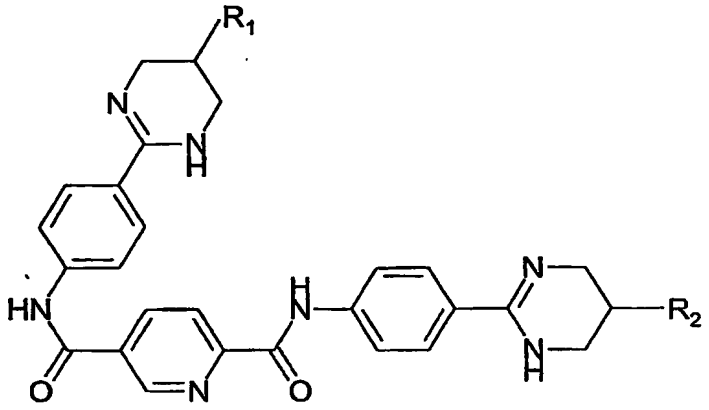
According to still a further aspect of the present invention is a method for the treatment of a tyrosine-kinase dependent disease or condition comprising administering a therapeutically effective amount of a composition comprising a compound of formula I further comprising a second compound selected from the group consisting of an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, an anti-proliferative agent, a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, and troponin-1, tamoxifen and raloxifene.

According to a further aspect of the present invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of formula I or II or pharmaceutically acceptable salts thereof in combination with a therapy selected from the group consisting of radiation therapy and chemotherapy.

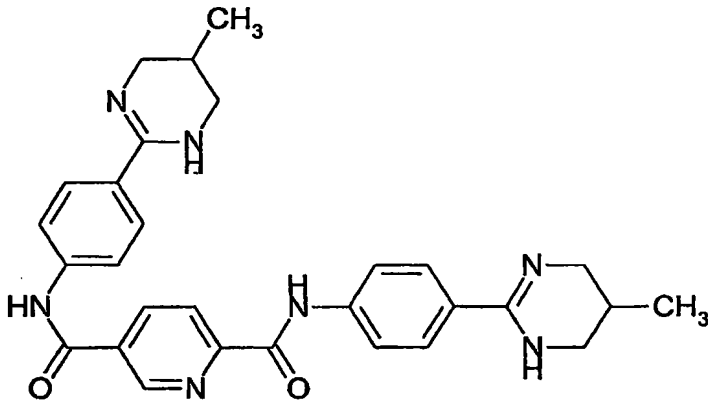
Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from said detailed description.

Detailed Description of the Preferred Embodiments

The compound of this invention is illustrated by Formula I or a pharmaceutically acceptable salt or stereoisomer thereof:



wherein R_1 and R_2 are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl; NZ_1Z_2, wherein Z_1 and Z_2 are



independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl.

Yet another embodiment of the present invention is a compound which is selected from the group consisting of

as well as pharmaceutically acceptable salts or stereoisomers thereof.

Using an in silico assay, the COTI-001 compound of the present invention has been demonstrated and predicted to have *in vitro* activity against a variety of cancerous cell types shown in Table 1. Also, while not explicitly shown, the COTI-001 compound of Formula I has predicted *in vitro* activity against HIV.

Included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Preferred cancers for treatment are selected from cancers of the breast, colon, prostate, gastric, melanoma, ovarian and leukemias. Another preferred form of cancer is chronic myelogic leukemia (CML).

The invention also encompasses pharmaceutical compositions comprising a compound of Formula I or II as well as pharmaceutically acceptable salts thereof for the treatment of HIV.

The compositions and methods of the invention can include a compound of Formula I or II.

Also included is a method of treating or preventing a tyrosine kinase-dependent disease or condition in a mammal which comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Formula I or II. The therapeutic amount varies according to the specific disease and is discernible to the skilled artisan without undue experimentation.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I or Formula II in combination with radiation therapy and/or in combination with a compound generally known to for use in selected cancers and selected from the group consisting of an

estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent and an antiproliferative agent. These and other aspects of the invention will be apparent from the teachings contained herein.

"Tyrosine kinase-dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases associated with tyrosine kinase activities include but are not limited to the proliferation of tumor cells.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E. L. Eliel and S. H. Wilen, Stereo-chemistry of Carbon Compounds, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_{1-10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on, as well as cycloalkyls such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydro-naphthalene, methylenecylohexyl, and so on. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl,

indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

The compounds of this invention may be prepared by employing reactions and standard manipulations that are known in the literature or exemplified in the experimental procedures.

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans, in the treatment of tyrosine kinase dependent diseases and in particular the treatment of various cancers.

The compounds of the instant invention may be administered to patients for use in the treatment of cancer.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with

known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadminsitered with radiation therapy. The synergistic effects of

inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO 00/61186). "Estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]ph- enyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5.alpha.-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylomithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin,

irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(c-hloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino- -13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunor- ubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(- 3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS 188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine- -2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methy- -1H,12H benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H) dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazo- le-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)-ethyl]-N-methylamino]ethyl]-5-[4-Hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,- 9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-

phenanthridiniu- m, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-py- razolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-- 9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acrid- ine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2- ,1-c]quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxy- cytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl) urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycer- o-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b] [1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-met- hoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example).

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-

dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino-)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epox- y-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH1382, genistein, ST1571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-- 7H-pyrrolo [2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyqui- nazoline, SU6668, ST1571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalaz- inamine, and EMD121974.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the

biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, partifcularly cancers involving inappropriate tyrosine kinase activity, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Examples. These Examples are described solely for purposes of

illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

Examples

The examples are described for the purposes of illustration and are not intended to limit the scope of the invention.

Methods of synthetic chemistry, protein and peptide biochemistry, molecular biology, and pharmacology referred to but not explicitly described in this disclosure and examples are reported in the scientific literature and are well known to those skilled in the art.

Example 1

Molecules with the potential target biological activity were analyzed in a validated *in silico* assay that is based on public domain National Cancer Institute *in vitro* anti-cancer data. The molecules are first decomposed to 110 descriptors using a proprietary CHEMSAS™ algorithm. This decomposition process results is a molecular data pattern of 110 variables that is then input into the *in silico* model. The output of the model is a prediction of the -Log(GI50) for the molecule(s) being analyzed against the specific cancer cell type in question i.e., breast cancer or leukemia, etc. A specific *in silico* assay was also developed for the leukemia cell line (i.e. K562) that over expresses the abnormal protein tyrosine kinase found in Chronic Myelogenous Leukemia (CML). Results of the *in silico* assay for molecular Formulas I and II in a number of cancer cell types are summarized below in Table 1.

Table One

Compound	leukemia	K562(CML)*	NSCLC**	SCLC***	Colon	CNS
Formula I/II	-5.39	-5.64	-4.89	-4.78	-5.16	-4.92

Compound	Melanoma	Ovary	Renal	Prostate	Breast
Formula I/II	-4.72	-4.84	-4.82	--5.13	-4.60

Note: Values in the table refer to the –Log(G150) as a molar concentration.

If –Log(G150)>-4.5 then the compound is likely to be inactive.

If –Log(G150)>-5 and <-4.5 then the compound is likely to have some *in vitro* activity.

If –Log(G150)<-5 then the compound is considered to have *in vitro* activity.

*K562 is a specific leukemia cell line for CML that over expresses the abnormal protein tyrosine kinase.

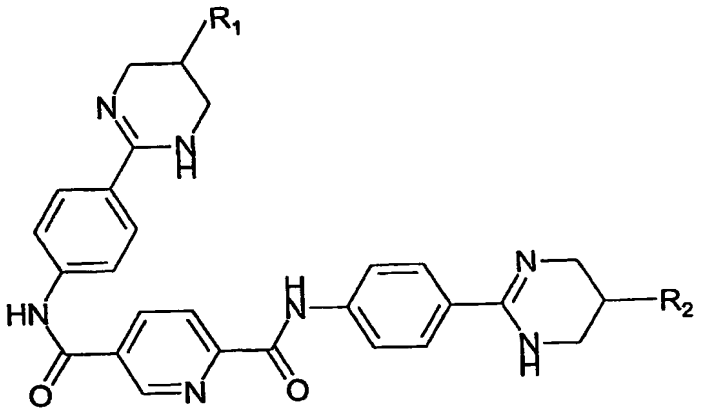
** NSCLC is a non small cell lung cancer

***SCLC is a small cell lung cancer

Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention.

Abstract

The present invention relates to uses of the compounds of Formula I as well as pharmaceutically acceptable salts and stereoisomers thereof in methods to treat a variety of tumors in mammals involving abnormal tyrosine kinase signalling, the compounds represented as:



wherein R_1 and R_2 are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl; NZ_1Z_2, wherein Z_1 and Z_2 are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl.